Exocrine pancreatic function in biliary tract pathology treated with the endoscopic methods

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Abstract

Purpose: Incidence of pancreatic exocrine insufficiency in biliary pathology is estimated for about 30%. The objective was to assess pancreatic exocrine function in biliary tract pathology (cholelithiasis, strictures) before and after endoscopic treatment.

Patients and methods: Twenty-eight patients with choledocholithiasis and its complications (19F/9M; aging 31-90 years, median: 69 years) were evaluated. Fecal elastase 1 concentration was measured using ELISA, before, early, and 6-8 weeks after endoscopic treatment. The inflammatory response of pancreas to the treatment was also assessed.

Results: Initial fecal elastase 1 concentration in patients (median 454 μg/g) was not significantly different as compared to the control (median 357 μg/g). Nine patients (32%) had low fecal elastase 1 concentration (below 250 μg/g) and out of them 6 had the concentration below 200 μg/g, suggesting impairment of exocrine pancreatic function. Endoscopic treatment was successful in 82% of patients. Pancreatic inflammatory response was noted only in one patient. After 6-8 weeks fecal elastase 1 concentration in the whole group of patients did not significantly change in comparison to the initial level. However, out of 9 patients with initially low fecal elastase 1 concentration (median 191 μg/g) at least in 6 pancreatic function improved (median 310 μg/g), $P<0.001$.

Conclusion: One third of the patients with biliary pathology had a low fecal elastase 1 concentrations, suggesting pancreatic dysfunction. In at least 2/3 of these patients successful endoscopic treatment of biliary pathology resulted in the significant increase of fecal elastase 1 concentration. Therefore, an additional positive effect of such treatment in some patients, could be an improvement of the exocrine pancreatic dysfunction.

Key words: exocrine pancreatic function, elastase 1, choledocholithiasis, endoscopic treatment.

Introduction

Choledocholithiasis occurs in 10-18% of patients with cholecystolithiasis [1] and may lead to cholangitis and postinflammatory stenosis. Stenosis of bile ducts can also be iatrogenic, e.g. formed after surgery [2]. Close anatomical vicinity and functional relationship suggest that diseases of bile ducts and pathological processes in the pancreas may exert a mutual effect on each other. Correlation of bile duct pathologies with chronic inflammatory pancreatic lesions are relatively little known. According to Misra et al. [3], abnormal pancreatograms were found in 48% patients with gallstones, of whom 16% had changes suggesting chronic pancreatitis (CP). Hardt et al. [4] observed features of CP in pancreatograms of 77% of patients with a history of gallstones and in 47% without the disease among patients submitted to endoscopic retrograde cholangiopancreatography (ERCP). Reduced concentration of fecal elastase 1 was more common in patients with a history of gallstones. Lamarque et al. [5] observed a reverse correlation, i.e. increased incidence of cholelithiasis in CP patients. However, some reports appear to negate the increased incidence rate of pancreatic pathology in cholelithiasis or etiological relationship between them [6]. Thus, the frequency and severity of pancreatic lesions, with a potential organ dysfunction accompanying bile duct disorders, still remain to be explained.

ERCP is a major diagnostic and therapeutic procedure used in pathologies of bile ducts and pancreas. Its diagnostic merits are associated with a simultaneously performed treatment

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for bile and pancreatic ducts, including sphincterotomy of the sphincter of Oddi, bile duct stone removal and insertion of prosthesis to dilate stenosis. The therapeutic efficacy of endoscopic procedures reaches 80-90% for bile duct stone removal and 89% for cancers that impair bile outflow [7,8]. The effect of endoscopic treatment for bile duct pathologies on a potential impairment of exocrine pancreatic function has not been elucidated yet.

A number of methods have been used to assess pancreatic secretion. In recent years, determination of fecal elastase 1 has become a commonly accepted standard. Elastase 1 is a pancreas-specific enzyme that does not undergo degradation during the intestinal passage [9]. Its concentration remains stable during therapeutic supplementation with pancreatic enzymes. The test is non-invasive and correlates well with those using secretin and cholecystokinin [10]. Its specificity reaches 93% while sensitivity is higher than that of the fecal chymotrypsin test [11], the respiratory test using triacylglycerols labeled with carbon 13C [12] or the para-aminobenzoic acid test [13].

Moreover, serum elastase 1 can be determined to evaluate acute pancreatitis (AP). In a study by Katsanos et al. [14], increase in serum elastase 1 level two hours after ERCP was found to be 100% specific in predicting acute pancreatitis (AP).

The current study objective was to assess exocrine pancreatic function based on the determination of fecal elastase 1 in patients with bile duct pathology (stones, stenosis) and to evaluate any immediate or distant in time changes in this function following endoscopic treatment of this pathology in the context of other laboratory tests used to control the disease and its treatment.

Patients and methods

Patients

Patients planned for ERCP were recruited for the study, except for those with suspected tumor of the head of the pancreas or bile duct carcinoma. The presence of bile duct pathology was established based on patients' history, physical examination, ultrasonography, features of cholestasis and/or cholangitis.

Twenty-eight patients (19 women, 9 men, aged 31-90 years, median 69 years) treated in the Department of Gastroenterology and Internal Medicine, Medical University of Białystok, were investigated. In 24 of them ERCP was indicated due to suspected choledocholithiasis and in 4 due to postsurgical stenosis of common bile duct (CBD). Four patients (2 with gallstones and 2 with CBD stenosis) had cholangitis. Sixteen patients showed a past history of cholecystectomy (12 with gallstones and all with CBD stenosis). Four suffered from type 2 diabetes (all with gallstones). An elevated bilirubin level was noted in 14/28 patients (50%).

All ERCP procedures were performed using an endoscope TJF-145 Olympus. Sphincterotomy was conducted with a sphincterotome KD-301Q-0330, stones were removed by means of balloons type B7-2Q, basket Dormia type FG-22Q-1 and lithotriptors type BML-3Q-1. Plastic prostheses (10F in diameter) were inserted into CBD, if indicated.

The study design

The concentrations of fecal elastase 1 as a measure of exocrine pancreatic function were estimated three times: before (determination 1) and twice after ERCP, combined with therapeutic procedure. Determination 2, to assess an immediate effect of the treatment was done in the first bowel movement, usually at the 1st to 3rd day following ERCP. Determination 3, to evaluate a long-term effect of the procedure was completed after 6-8 weeks.

Other measurements included determination of serum elastase 1 concentration [14], routine laboratory tests for the activity of α-amylase in serum and urine, serum bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotranferase (AST) and leucocytosis. Serum was collected prior to ERCP (determination 1), on day 2 (determination 2) and 6-8 weeks after ERCP combined with therapeutic procedure (determination 3).

Elastase 1 was determined by ELISA using two monoclonal antibodies which bind to strictly defined epitopes of the enzyme (ScheBo Tech kit).

Control group

Ten healthy volunteers (6 women, 4 men, aged 27-75, median 56) were recruited in order to determine normal fecal and serum elastase 1 levels.

The protocol was accepted by the local Bioethics Committee. Patients gave their written informed consent to participate in the study.

Statistical analysis

Statistical analysis was carried out using the Statistica 6.0 program. The Kolgomorov-Smirnov test was applied to examine the normality of distribution of variables. As normal distribution was not confirmed, the U Mann-Whitney test was applied to assess statistically significant differences between the study and control group. The Wilcoxon test (sequence within pairs) was performed to assess the respective parameter in time. The values were presented as median as well as 25 and 75 percentile. The correlation and regression coefficients were calculated according to Pearson. $P \leq 0.05$ was considered statistically significant.

Results

Endoscopic procedures

Bile duct cannulation during ERCP was successful in 26/28 patients (92%). Twenty-three patients underwent sphincterotomy, three had sphincterotomy performed earlier (2 endoscopic, 1 surgical). CBD stenoses were balloon-dilated and prostheses were inserted. Bile duct stones, macroscopically visible in 19 patients, were evacuated using a Dormia basket and a balloon, and in 4 cases mechanical lithotripsy was carried out. In total, the procedure was fully successful in 23 patients (82%). Three patients developed complications: bleedings from the papilla of Vater in 2 cases (7%), which were treated endoscopically with adrenaline solution during the same procedure, and mild AP in one case.

***Table 1*. Biochemical parameters of the patients with bile duct pathology. Medians (in brackets 25th and 75th percentile) are reported**

Parameter	Measurement 1, before endoscopic procedure (n=28)	Measurement 2, early# after procedure (n=25)	Measurement 3, 6-8 weeks after procedure (n=24)
Fecal elastase 1 (μg/g)	454 (224, 572)	405 (319, 540)	448 (286, 515)
Serum elastase 1 (ng/mL)	1.13 (0.83, 1.42)	1.07 (0.87, 1.63)	1.09 (0.89, 1.49)
Serum α-amylase (IU/L)	40 (30, 46)	43 (31, 57)	40 (36, 52)
Urine α-amylase (IU/L)	140 (63, 229)	202 (129, 313) * P<0.05	Not determined
Serum bilirubin (mg/dL)	1.33 (0.95, 3.87)	1.55 (1.06, 2.74)	0.97 (0.78, 1.14) ** P< 0.001 *** P< 0.001
Alkaline phosphatase (IU/L)	261 (149, 361)	224 (138, 321) * P<0.05	103 (92, 120) *** P< 0.001
AST (IU/L)	59 (25, 115)	54 (28, 105)	32 (24, 42) ** P< 0.005 *** P< 0.01
ALT (IU/L)	83 (24, 204)	68 (21, 126)	36 (23, 44) **P< 0.001 *** P< 0.005
White blood cell count (x10^3/μL)	7.76 (5.60, 9.41)	6.79 (5.23, 8.30)	5.86 (4.95, 7.49) *** P< 0.05

fecal elastase 1-3 days (the first bowel movement), other parameters in the next day after endoscopic procedure; * (difference between 1 and 2 analysis); ** (difference between 2 and 3 analysis); *** (difference between 1 and 3 analysis)

Complete laboratory tests were done in 28 patients (100%) prior to the procedure (determination 1); in 25 at determination 2 (89%) and in 24 at determination 3 (86%); the remaining patients did not come for a check-up.

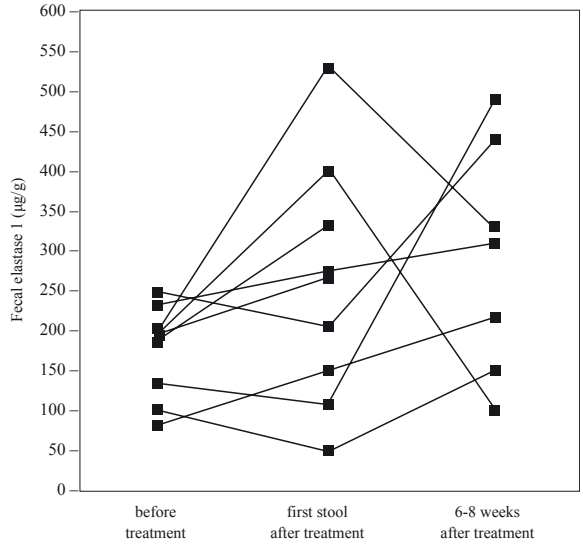
Fecal elastase 1

In the whole group, fecal elastase 1 concentration prior to the procedure (median 454 μg/g feces; 25 and 75 percentile, 224 and 572 μg/g, respectively) did not differ significantly from the control values (median 357 μg/g; 284 and 391μg/g). However, in 6 patients (21%) fecal elastase 1 level below 200 μg/g was noted. In other 3 cases, the concentrations ranged between 200 and 250 μg/g. In total, concentrations below 250 μg/g (median 191; 128 and 201 μg/g) were found in 9 patients (32%). It is noteworthy that a slightly higher levels were found in a group of 9 patients suffering from jaundice (median 467; 293 and 571 μg/g); however, in comparison with the control the difference was not statistically significant.

In the first stool following the procedure, elastase 1 concentration was reduced in 12 patients (by 103 μg/g on average), and increased in 13 (by 115 μg/g on average). The changes were not correlated with those noted in serum bilirubin. The overall concentration in the whole group of patients did not differ statistically significantly as compared to determination 1 (median 405 μg/g; 319-540 μg/g).

At determination 3, 6-8 weeks after endoscopic procedure, fecal elastase 1 level (median 448 μg/g; 286-515 μg/g) did not differ statistically significantly as compared to the 1st and 2nd measurement. However, in 6 from 9 patients (67%) with lowered elastase 1 level prior the procedure its level increased (median 310; 179 and 381 μg/g). In one patient (with unsuccessful removal of stones from bile ducts after sphincterotomy), a distant check-up revealed a further decrease in elastase 1. Two patients did not come for the long-term check-up, but in both of them fecal elastase 1 was higher at determination 2 than at baseline. Moreover, in one patient with normal fecal elastase at baseline, the concentration was below the norm 6-8 weeks after the procedure (*Tab. 1*, *Fig. 1*).

***Figure 1*. Fecal elastase 1 concentration in the patients with its initial low value: before and after endoscopic treatment of bile duct pathology**



Serum elastase 1

The median value of serum elastase 1 in the control group was 1.35 ng/mL; (percentile 25 and 75; 1.02 and 1.95). Baseline serum elastase 1 in the group of patients was 1.13 ng/mL (0.83 and 1.42) and did not differ significantly as compared to the control.

One day after the procedure, serum elastase 1 did not differ statistically from the values noted at determination 1 – median 1.07 (0.87 and 1.63) ng/mL, slightly exceeding the norm suggested by the kit producer only in sole patient with mild AP. Serum elastase 1 on day 2 strongly correlated with the simultaneously determined activities of α-amylases in serum and urine (r=0.67 and r=0.66), AST (r=0.77) and ALT (r=0.61). All the correlations were statistically significant (P≤0.001). Moreover, elastase 1 on day 2 showed a weak but statistically significant correlation with the activity of alkaline phosphatase (r=0.41, P<0.05). After 6-8 weeks, the median of serum elastase 1 was 1.09 ng/mL (0.89 and 1.49) (with no significant differences between determination 1 and 2), (*Tab. 1*).

Activity of α-amylase

Serum activities of α-amylase did not differ significantly between all the three determinations. After the procedure, four patients developed transitory hyperamylasemia. In one of them the activity of α-amylase was 5-times the norm. The median of α-amylase activity in urine at determination 2 (202 IU/L; 129 and 313 IU/L) was higher than at determination 1 (140 IU/L; 63 and 229 IU/L), (P<0.05), (*Tab. 1*).

Bilirubin concentration

The median of baseline bilirubin was 1.33 mg/dL (0.95 and 3.87), while its level on day 2 increased to 1.55 mg/dL (1.06 and 2.74). After 6-8 weeks, the concentration decreased to 0.97 mg/dL (0.78 and 1.14), as compared to the laboratory norm below 1.2 mg/dL. The elevated bilirubin levels prior to endoscopic procedure were observed with similar frequency both in patients with low and normal fecal levels of elastase 1 (4/9 patients with low and 10/19 with normal level). The differences between determination 2 and 3 and between 1 and 3 were statistically significant (P<0.001), (*Tab. 1*).

Activity of alkaline phosphatase

The activity of alkaline phosphatase (norm 45-123 IU/L) was reduced from 261 IU/L (percentile 25 and 75, respectively, 149 and 361 IU/L) prior to the procedure to 224 IU/L (138 and 321 IU/L) on day 2 (P<0.05) and to 103 IU/L (92 and 120 IU/L) 6-8 weeks after the procedure (P<0.001), (*Tab.1*).

Activity of aminotransferase

The activities of AST and ALT were as follows: 59 IU/L (25 and 115 IU/L) and 83 IU/L (24 and 204 IU/L) at determination 1, 54 IU/L (28 and 105 IU/L) and 68 IU/L (21 and 126 IU/L) at determination 2; 32 IU/L (24 and 42 IU/L) and 36 IU/L (23 and 44 IU/L) at determination 3 (norm 5-50 IU/L). The differences were statistically significant between determination 1 and 3 (P<0.05 for AST and P<0.005 for ALT) and between determination 2 and 3 (P<0.005 for AST and P<0.001 for ALT), (*Tab. 1*).

Leucocytosis

No significant differences were observed between the values of leucocytosis before the procedure (median $7.76\times10^3/\mu L$; 5.6 and $9.41\times10^3/\mu L$) and a day after the procedure (median $6.79\times10^3/\mu L$; 5.23 and $8.30\times10^3/\mu L$). However, 6-8 weeks later a statistically significant decrease was noted in comparison to baseline (median $5.86\times10^3/\mu L$; 4.95 and $7.49\times10^3/\mu L$; p<0.05), (*Tab. 1*).

Discussion

Cholelithiasis is the most common pathology within the biliary ducts, affecting 15% of the population (1). In 10-18% of patients, cholecystolithiasis is accompanied by bile duct stones. Choledocholithiasis may induce biliary colic and cause life-threatening complications, such as mechanical jaundice, cholangitis with postinflammatory stenoses, secondary biliary cirrhosis with portal hypertension and acute pancreatitis. It is therefore suggested that every case of choledocholithiasis should undergo treatment in order to prevent potential complications [1,15]. The effect of cholepathies on the exocrine function of the pancreas still remains a subject of controversy [3-6].

In all our patients, ERCP was performed with the purpose to treat biliary duct pathology. The efficacy of such procedures as cannulation (92%), stone removal or stenosis correction (82%) did not differ from the world statistics [7]. Once the indications had been established, sphincterotomy of the sphincter of Oddi was performed in the patients who had never undergone this procedure before. Although sphincterotomy increases the risk of complications, it has also positive effects. It has been reported that spincterotomy may lead to the evacuation of stones or biliary sludge in 55% of patients without visible pathological changes in cholangiogram [16]. According to some data, even up to 84% of stones in biliary colic and 55% in mechanical jaundice will spontaneously pass into the duodenum and are thus not detected [17]. In our study, the presence of macroscopically visible gallstones was confirmed in 19/24 patients (79%).

For 200 μg/g accepted as the borderline norm, determination of elastase 1 in feces exhibits 100% sensitivity for severe and moderate exocrine pancreatic insufficiency as well as 25-63% sensitivity for mild insufficiency [10,11]. Hamwi et al. [18] suggest that the borderline value can be + 25% of the recommended concentration of this enzyme due to its possible fluctuations in various stool samples from one patient.

Considering normal fecal elastase 1 levels to be over 250 μg/g, we found abnormal values in 9/28 patients (32%), including 6 (21%) with the concentrations below 200 μg/g, which may suggest moderate or severe exocrine pancreatic insufficiency. A similar tendency was observed by Hardt et al. [4], who noted reduced concentrations of elastase 1 in 30.8% of patients suffering from gallstones.

Pancreatic secretion depends on a number of factors. A reduction in fecal elastase 1 in patients with choledocholithiasis might be caused by mechanical obstruction in the outflow of pancreatic juice with bile. However, elevated bilirubin levels

were observed with similar frequency both in patients with low and normal fecal levels of elastase 1. Moreover, the mean fecal elastase 1 concentration was the highest in jaundice patients. Even though the difference was not statistically significant, its direction was consistent with *in vitro* observations and some animal studies, in which cholestasis led to an increase in basal and cholecystokinin-stimulated pancreatic secretion [19]. It thus seems that disturbances of pancreatic juice outflow are not the only factor responsible for the reduction in fecal elastase 1 in patients with bile duct pathology.

Removal of stones from biliary ducts is only the evacuation of the final product of complex pathological processes. Choledocholithiasis recurs in approximately 10% of patients within 6 years after surgery [20]. It cannot be excluded that not only gallstones but also various factors promoting this pathology may affect pancreatic function. Inflammatory reaction, fibrosis and formation of stenosis at the level of papilla of Vater caused by macroscopically visible gallstones or by even more common microlithiasis are the likely pathogenetic link in CP. Stenosis may lead to mild obstructive pancreatitis and cause a gradual loss of endocrine and exocrine function of the organ [4,21]. Elimination of stenosis should theoretically improve the exocrine function of the pancreas.

In the current study, fecal elastase 1 remained stable in all the three determinations. Although in the respective patients the levels of fecal elastase 1 changed in comparison to baseline values, there was a strong statistically significant correlation between determination 1 and 2 as well as 1 and 3, which suggests certain individual stability of secretion. Endoscopic treatment of biliary duct pathologies did not significantly change the exocrine function of the pancreas in the overall study population. However, in 6/9 patients whose baseline fecal elastase 1 levels were found to be low, an increase was noted at determination 3, and in 4 out of these 6 the values were normalized. In two out of these 9 patients, fecal elastase 1 reached normal values in the first stool after endoscopic treatment, but they did not come for a check-up 6-8 weeks later for further assessment. In one patient (with unsuccessful removal of stones from bile ducts after sphincterotomy) a further decrease of fecal elastase 1 level was noted during long-term check out.

The current findings seem to indicate a relationship between endoscopic treatment of biliary pathology and improvement of exocrine function of the pancreas. Our results correspond to those reported by Ewald et al. [22], who observed an increase in fecal elastase 1 in patients after endoscopic sphincterotomy performed due to dysfunction of the sphincter of Oddi. The increase was most significant in patients with pathologically low baseline levels of elastase 1. Also Doubilet et al. [23] showed improvement or even regeneration of exocrine function of the pancreas after surgical sphincterotomy.

After the procedure, four patients developed transitory hyperamylasemia. Although on day 2 serum elastase 1 correlated strongly with the increase in serum and urine activities of α-amylase, its concentration slightly exceeded the norm suggested by the kit producer just in one patient with mild AP, according to Cotton`s et al. [24] criteria.

Katsanos [14] observed higher specificity but lower sensitivity of serum elastase 1 in the detection of AP after ERCP. Our findings did not indicate on any prevalence of serum elastase 1 as compared to α-amylase in the detection of AP after ERCP.

Conclusions

No significant exocrine pancreatic dysfunction determined as fecal elastase 1 concentration was found in the overall study group of patients with biliary duct pathology, as compared to the control. However, in 32% of cases fecal elastase 1 level was below 250 μg/g, which suggests exocrine insufficiency of the pancreas. Endoscopic treatment of biliary duct pathology resulted in a significant reduction in cholestase parameters, but did not affect the mean elastase 1 concentration in the whole group. Nevertheless, at least 2/3 of patients who prior to the procedure had fecal elastase 1 below 250 μg/g showed its increased levels 6-8 weeks following endoscopic treatment. This may suggest improvement in pancreatic secretion due to endoscopic treatment for biliary duct disorder and its complications.

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